IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Van Beusechem

Examiner: Scott Long

Serial No: 10/501,407

Group Art Unit: 1633

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For: VIRUSES WITH ENHANCED LYTIC POTENCY

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Lauren T. Emr
(Printed Name)

Signature: /Lauren T. Emr/

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF FRANK MCCORMICK, PHD, FRS UNDER 37 C.F.R. § 1.132

I, Frank McCormick, PhD, FRS, declare as follows:

1) I am Director of the Helen Diller Family Comprehensive Cancer Center & Cancer Research Institute of the University of California, San Francisco (UCSF). I was founder and Scientific Director of Onyx Pharmaceuticals and as such have been actively involved in pre-clinical and clinical development of oncolytic adenoviruses, amongst which the ONYX-OIS product which has been tested in various clinical studies. I have been practicing in the field of adenovirus gene therapy for 18 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2) I have read U.S. Patent Application No. 10/501,407 and the related office actions dated July 6, 2010 and December 2, 2010. In particular, I have read the comments from the examiner that claims 26-35 and 38-40 are obvious in view of Curiel et al. (US-6,824,771) and

Xu et al. (Human Gene Therapy 1997; 8:177-185), and that claims 36-37 are obvious over the same references also in view of Lin et al. (Cancer Research 2000; 60:5895-5901). I have also read the response by the applicant thereto filed on November 8, 2010, and the references Curiel et al., Xu et al., and Lin et al. I understand that similar objections have been raised by the examiner based on the combination of Hallenbeck et al (Human Gene Therapy 1999; 10:1721-1733) and Lin et al.; and Fueyo et al. (Oncogene 2000; 19:2-12) and Lin et al. Therefore, I have also read Hallenbeck et al and Fueyo et al.

3) The unexpected discovery that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from available research publications, at the time the instant application was filed. Specifically, it was not predictable from the teachings of Curiel et al., Xu et al., or Lin et al., or from a combination thereof. The Hallenbeck et al. and the Fueyo et al. references resemble the Curiel et al reference in that they address oncolytic viruses, albeit that the specific oncolytic virus is different from the one discussed by Curiel et al.

4) The fact that the oncolytic virus was slightly different is not of particular relevance. As stated above, the finding that the addition of a gene expressing p53 to a conditionally replicating adenovirus increased efficacy was, in my opinion, highly novel and certainly not predictable from previous research publications.

5) On the contrary, at the time the instant application was filed, it was expected that restoration of functional p53 would suppress viral replication, as suggested by Hermiston and Kuhn (Cancer Gene Therapy, 2002; 9:1022-1035) and others. This is because p53 is actively degraded during viral replication, and adenoviruses that fail to degrade p53 are defective for replication in normal primary human cells (O'Shea et al., Cancer Cell, 2004; 6:611-623). This view was re-enforced recently by O'Shea and coworkers (Soria et al., Nature 2010; 466: 1076-1081) who showed that adenoviral E4 proteins contribute to inactivation of p53 during infection, in addition to the well-known effect of EIB 55K on p53 degradation. Therefore, restoration of

functional p53 would be expected to suppress virus replication rather than enhancing it. A copy of Soria et al. is attached as Exhibit B.

6) Another surprising aspect of the instant application's discovery is that p53 expressed in an adenovirus remains functional at all. Adenoviruses shut down host protein synthesis and synthesis of viral genes expressed from certain early promoters. It was therefore unexpected that p53 could remain functional (documented in van Beusechem et al., Cancer Research 2002; 62:6165-6171) and promote expression of downstream genes. The recent work of Soria et al. cited above also underscores the fact that adenoviruses encode multiple mechanisms to eradicate and inactivate p53 during infection: the activity demonstrated by the instant invention was therefore unexpected for several distinct reasons.

7) The idea that direct, forced, expression of p53 in a p53-negative tumor cell promotes growth arrest, or cell death, has been well established for many years. However, this effect is clearly distinct from the novel role of p53 in promoting virus replication, as discovered in the instant application. The importance of the instant invention is based on the presumption that clinical efficacy depends on robust virus replication and infection of multiple tumor cells, rather than direct killing of a single transduced cell by a non-replicating viral vector.

8) For these reasons, I believe that the concepts underlying the instant patent application are novel and were not at all predictable/obvious based on prior publications or disclosures, at the time of the invention.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed: _____ Dated: 3/19/04

Dr. Frank McCormick